

### **REMARKS**

The Office Action of December 17, 2009, has been carefully studied. Claims 1-17 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration and formal allowance of the claims.

### **Election/Restriction**

It is noted with appreciation that claims 10 and 11 have been rejoined for examination.

### **Claim Amendments**

Claims 1-9 and 11-17 have been amended to recite the salt of the hyaluronic acid-methotrexate conjugate. Support for these amendments can be found in the specification as filed at paragraph [0074]. Claims 11-17 have been amended to change the term "hyaluronic acid" to "hyaluronic acid, derivative, or salt thereof" so as better to conform to the recitations in claim 1.

The definition for Q<sub>2</sub> in claim 10 has been amended as follows:  
"Q<sub>2</sub> is a C<sub>2-20</sub> alkylene, wherein the alkylene optionally has 1 to 4 oxygen atoms inserted thereinto and/or is optionally substituted by a C1-6 alkoxy carbonyl group." Claim 11 has not been so amended.

### **Art Rejections**

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snow et al., WO 94/13327 in view of Nogusa et al., US 5,688,931.

This rejection is respectfully traversed.

The presently claimed invention relates to a conjugate of hyaluronic acid and methotrexate wherein methotrexate is conjugated with a carboxyl group of hyaluronic acid, a hyaluronic acid derivative, or a salt thereof, through a linker containing a peptide chain consisting of 1 to 8 amino acids; an intermediate for preparing the conjugate; and a process for preparing the conjugate.

The claimed conjugate has many advantages over the prior art. First, as described in paragraph [0044] in the present specification, in the treatment of joint disease, the conjugate has both the pain-eliminating effect of hyaluronic acid (HA) as well as the synovitis-alleviating effect of methotrexate (MTX).

Further, as described in paragraph [0045] of the present specification, when administered to the knee joint of OA or RA patients, the conjugate accumulates in synovial tissue and is gradually incorporated into synovial cells, where it releases MTX to exert a persistent synovitis-suppressing effect, resolving a problem that MTX rapidly disappears from a joint cavity, as described in paragraph [0010]. The 'HA in the conjugate enables the conjugate

to accumulate in synovial tissue, and thus functions as a drug delivery system for MTX. This makes it possible to administer a greatly reduced dose of MTX compared to that for oral administration thereof, and can thereby eliminate problems of systemic side effects, which may occur with oral administration of MTX. Further, the HA and MTX can exert pharmacological effects that are different from each compound alone, and a synergistic beneficial effect is obtained. In the working examples, particularly as shown in Figures 2 and 3, it is shown that the synergistic effect of the conjugate is beyond the expectations of those skilled in the art based on the effects of MTX or Ha alone.

Neither the structure nor the effects of the herein claimed invention are obvious over the combination of Snow and Nogusa.

Snow is directed to a therapeutic treatment and diagnostic imaging of cancer by means of a tumor targeted sequential delivery system (please refer to "Field of the Invention"). Snow discloses MTX analogs comprising peptide linkages that are conjugated to certain compounds, such as polysaccharides. However, there is nothing in Snow that teaches or suggests that the polysaccharide can be hyaluronic acid.

Nogusa relates to a polysaccharide derivative which can accumulate at a tumor site (please see column 2, lines 4-8). The polysaccharide is considered to be useful in treating a tumor. Nogusa discloses a conjugate of hyaluronic acid and doxorubicin, a different drug than methotrexate.

The Examiner alleges that it would have been obvious to one skilled in the art to combine the teachings of Snow with those of Nogusa to arrive at the herein claimed conjugate. However, it should be noted that there are many compounds disclosed that could be combined to form a conjugate. The term "polysaccharides" in Snow encompasses a great many compounds, and Nogusa discloses many compounds to be combined with polysaccharides. There is nothing in the combination of Snow and Nogusa that suggests combining the compounds to obtain the conjugate claimed herein.

There is no indication of how one skilled in the art would select the two compounds conjugated herein from the basket disclosures of Snow and Nogusa.

The possibilities within the basket or shotgun disclosure are practically infinite rejection, obviousness is

The situation is not unlike that raised in *Ex parte Garvey*, 41 USPQ 583 (1939) in which the Board said:

... The likelihood of producing a composition such as here claimed from a disclosure such as shown by the Dykstra patent would be about the same as the likelihood of discovering the combination of a safe from a mere inspection of the dials thereof.

\* \* \*

... However, as in the Dykstra et al disclosure, the proper one of a large number of possible permutations must be chosen to bring the disclosure within the terms of the claims on appeal. Under such

circumstances, we do not feel that the patent is a fair reference...

None of the above-mentioned effects of the conjugate claimed herein would have been obvious from the disclosures of Snow and Nogusa. Both Snow and Nogusa relate to treating tumors, which is completely different from the pain-eliminating effect and the synovitis-alleviating effect in joint-related diseases. Additionally, there is nothing in the combination of Snow and Nogusa that teaches or suggests the above-mentioned synergistic effect of the claimed conjugate.


Since the claimed conjugate is not obvious, it is respectfully submitted that the intermediate of the conjugate (Claim 10) and the process for producing the conjugate (claim 11) should also be not obvious. It should be noted that the amendment made to claim 10 removes the compound disclosed in Snow (compound 11 in Scheme 4, page 42).

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

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Respectfully submitted,

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